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TELEFAX

Date: June 21, 2004 **Total pages:** 23

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Our Docket No. MIT 6210
Your Docket No. **Client/Matter No.** 701350-8

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MESSAGE:
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Linda G. Cima, Edward W. Merrill and Philip R. Kuhl

Serial No.: 09/398555 Art Unit: 1654

Filed: March 3, 1995 Examiner: Jeffrey E. Russell

For: Cell Growth Substrates With Tethered Cell Growth Effector Molecules

PTO/SB/21 (08-03)
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TRANSMITTAL FORM
(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	08/398,555
Filing Date	March 3, 1995
First Named Inventor	Linda G. Cima
Art Unit	7254
Examiner Name	Jeffrey E. Russel
Attorney Docket Number	MIT 6210

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
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- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please identify below): Request for Oral Hearing

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Patrea L. Pabst, Esq., Reg. No. 31,284 Pabst Patent Group LLP 400 Colony Square, Suite 1200, Atlanta, GA 30361
Signature	
Date	June 21, 2004

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Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 290

Complete if Known

Application Number	08/398,555
Filing Date	March 3, 1995
First Named Inventor	Linda G. Cima
Examiner Name	Jeffrey E. Russel
Art Unit	7254
Attorney Docket No.	MIT 6210

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims	7	-20** =	0	X =	
Independent Claims	2	-3** =	0	X =	
Multiple Dependent				=	

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	290
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

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SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Patrea L. Pabst	Registration No. (Attorney/Agent)	31,284	Telephone	(404) 879-2151
Signature				Date	6/21/2004

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REQUEST FOR ORAL HEARING BEFORE THE BOARD OF PATENT APPEALS AND INTEFERENCES

Docket Number (Optional): MIT 6210

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Signature: Ronna Berman

Typed or printed name: Ronna Berman

In re Application of: Linda G. Cima

Application Number: 08/398,555

Filed: March 3, 1995

For: CELL GROWTH SUBSTRATES WITH TETHERED CELL GROWTH EFFECTOR MOLECULES

Art Unit: 1654

Examiner: Jeffrey E. Russel

Applicant hereby requests an oral hearing before the Board of Patent Appeals and Interferences from in the appeal of the above-identified application.

The fee for this Request for Oral Hearing is (37 CFR 1.17(d)) $ 290.00

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account. I have enclosed a duplicate copy of this sheet.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 50-3129 . I have enclosed a duplicate copy of this sheet.

☐ A petition for an extension of time under 37 CFR 1.136(b) (PTO/SB/23) is enclosed. For extensions of time in reexamination proceedings, see 37 CFR 1.550.

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I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record. Registration number 31,284

☐ attorney or agent acting under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a). _____

Signature

Patrea L. Pabst
Typed or printed name

(404) 879-2151
Telephone number

June 21, 2004
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Linda G. Cima, Edward W. Merrill and Philip R. Kuhl		
Serial No.:	09/395,555	Art Unit:	1654
Filed:	March 5, 1995	Examiner:	Jeffrey Russell
For:	*CELL GROWTH SUBSTRATES WITH TETHERED CELL GROWTH EFFECTOR MOLECULES*		

Mail Stop Reply Brief - Patents
Commissioner for Patents
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REPLY TO EXAMINER'S ANSWER

Sir:

This is a reply to the Examiner's Answer mailed April 20, 2004 in the above identified patent application. A request for Oral Hearing is enclosed along with the appropriate fee for a large entity. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

Appellants have appealed the final rejection of claims 14-17 and 32-34 in the Office Action mailed October 3, 2003. A Notice of Appeal was mailed on January 2, 2004. An Appeal Brief was mailed March 2, 2004.

(1) STATUS OF AMENDMENTS

The amendment after final rejection filed on February 9, 2004 has been entered.

(2) ARGUMENTS

Appellants affirm all arguments set forth in the Appeal Brief. The following remarks are submitted in response to the Examiner's Answer.

Response to Examiner's Answer

(a) Rejections Under 35 U.S.C. § 103

Claims 14-16 and 33 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,370,681 to Herweck et al. ("Herweck") in view of U.S. Patent No. 5,171,264 to Merrill ("Merrill"). This rejection is improper since Merrill discloses water insoluble hydrogels; and Appellants use growth factors immobilized on water soluble tethers

The PEO star molecules described by Merrill are not water soluble as stated by the Examiner. On the contrary, the prior art PEO star molecules are ***water insoluble hydrogels*** (abstract; column 1, lines 21-25; and column 3, lines 26-31). Hydrogels are polymers which swell extensively in water but are not water soluble. The hydrogels described by Merrill are prepared by cross-linking the PEO chains via electron radiation resulting in water-insoluble PEO. Such a method of preparation should result in a composition in which the PEO arms are much less mobile than the compositions claimed herein which do not use a hydrogel composition. The Appellants disclose and claim a composition in which the PEO arms are not cross-linked and thus are water soluble. This results in polymer arms that are fully extendable and highly mobile. The mobility of these arms allows the tethered growth factors to cluster on the surface of the cell and enhance cell growth (page 6, lines 19-23). One of ordinary skill in the art would not be motivated to combine the ***water-insoluble hydrogels*** of Merrill with the

biocompatible materials and growth factors of Herweck to prepare compositions comprising growth effector molecules covalently linked to highly flexible *water-soluble tethers* which are not hydrogels and therefore cluster on the surface of the cell to enhance target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to the substrate.

Claim 17 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Herweck in view of Merrill and U.S. Patent No. 5,522,895 to Mikos ("Mikos").

Claim 17 is dependent upon claims 14-16 and 33, which, as discussed above, are not obvious over Herweck in view of Merrill since Merrill discloses water-insoluble hydrogels not tethers. Mikos does not describe the elements missing from the combination of Herweck and Merrill.

(b) Rejections Under the Doctrine of Obviousness-type Double Patenting

1. *The Correct Test is a Two-way Patentability Test*

The Examiner used a "one-way" patentability test to support the rejection of claims 14-17 and 32-34 under the doctrine of obviousness-type double patenting over the earlier issued patents claiming priority to this application. In *re Berg*, 46 USPQ2d 1226 (Fed. Cir. 1998), the Court held that the "two-way" exception applies (1) when the Appellant could not avoid separate filings, and (2) when the PTO controlled the rates of prosecution to cause the later filed species claims to issue before the claims for a genus in an earlier application.

A two-way patentability test is appropriate when an inventor or assignee files a patent application claiming an improvement or combination invention after a patent application

claiming the basic or subcombination, but the second-filed application issues first through no inventor or assignee fault. See *re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991).

The Examiner's use of the one-way test assumes the claims of the latter filed but earlier issued patents are species of the genus defined in the pending application. As discussed below, this assumption is not correct.

2. Prosecution of the Present Application was Subject to Administrative Delay.

The present application was subject to administrative delay on behalf of the PTO which caused the later filed improvement applications to issue before the earlier filed basic application.

U.S. Patent Nos. 5,906,828 and 6,045,818 were filed on October 8, 1997 and November 25, 1998. They issued on May 25, 1999 and April 4, 2000, respectively. The present application was filed on March 3, 1995 and has been appealed twice. The first Notice of Appeal was filed on September 24, 1997. The BPAI mailed their decision on July 27, 2001, almost four years later, remanding to the Examiner the rejection of claims 14-17, and questioning certain rejections and interpretations of the prior art. The first office action after appeal was mailed on March 29, 2002, more than 8 months after the BPAI's decision. After three more years of prosecution, the case has again been appealed.

This history establishes that it has taken an unusual amount of time both to get office actions and for decisions on appeal to be reached. These delays clearly constitute administrative delay for purposes of which test is appropriate for determining obviousness-type double patenting.

3. *Regardless of the Test, the Claims in this Application are Not Obvious*

The law is quite clear that, for the Patent Office to establish a *prima facie* case of obviousness of claimed subject matter, the prior art references relied upon must provide *both* a suggestion to make the claimed invention and a reasonable expectation of success. It is also clear that the whole field of the invention must be considered, including those publications which teach away from the claimed invention. Where a one way-way obviousness test is required, the Graham obviousness analysis must be applied with the application claims in issue. A two-way obviousness determination requires the Graham obviousness analysis be applied first with the application claims as the claims in issue and second with the patent claims as the claims in issue. The disclosure of the patent may not be used as prior art in either test.

An obvious-type double patenting rejection is inappropriate where either analysis in the two-way test compels a conclusion that the invention defined in the claims in issue is not an obvious variation of the invention defined in the other patent.

a. Claims 14-17 and 33 are not Obvious over U.S. Patent No. 5,906,828 (Cima '828) in Combination with Kausch and Nitecki.

As noted in the Appeal Brief (see page 17-19), claims 1-4 of Cima '828 define a method of growing eukaryotic cells in a patient in need of cell growth comprising a composition comprising a biocompatible solid substrate, biocompatible branched water-soluble polymeric tethers, and growth effector molecules. Claims 14-17 and 33 of the present application define a method of growing eukaryotic cells comprising a composition comprising a biocompatible substrate, biocompatible polymeric tethers, and growth effector molecules. A side-by-side

comparison of the claims is shown below. As is evident from the comparison, there are two major differences between the claims which are not obvious from the other claims:

The Cima '828 claims are drawn to a substrate that is implanted into a patient

The Cima '828 claims are drawn to a substrate comprising branched, water soluble tethers having multiple growth factor molecules attached thereto.

The '799 claims on appeal are drawn to a biocompatible substrate, with no reference to implantation.

The '799 claims on appeal are drawn to a substrate having a defined density of growth factors attached to one end of polymeric tethers and to the substrate at the other end.

The examiner has cited no art that would lead one skilled in the art to substitute the branched tethers of the '828 claims for the tethers of the '799 application so that one would look only at the final concentration of growth factors, not the final density of tethers bound to substrate

The examiner has cited no art that would lead one skilled in the art to substitute density of tethered growth factors on a substrate for growth factors attached to branched molecules in a desired density. On a practical basis, the latter composition allows one to be effective by controlling only the number of growth factor molecules bound, not requiring the substrate to have to first have the requisite number of tethers bound, then the requisite number of growth factor molecules bound. Moreover, the length of the tether is of critical importance because it must be sufficient to allow the growth factor a sufficient range of motion to effectively bind to a cell surface receptor. The minimum tether length depends on the nature of the tether. A more

flexible tether (i.e. one without branching) will function well even if the tether length is relatively short.

Therefore using either a one-way or a two-way test, the claims are not obvious over each other. Another point is that the examiner believed the claims in the '828 patent to be novel and non-obvious over the art cited herein against the claims in issue, therefore leading to the conclusion that the examiner at least believed that the different limitations were novel and non-obvious.

Cima '828: Claim 1	'555 Application: Claim 33
1. A method for growing eukaryotic cells comprising (a) bringing into contact the cells and a composition comprising a biocompatible solid substrate, ***biocompatible branched*** water soluble polymeric tethers, and growth effector molecules, wherein one end of each tether is covalently linked to the substrate, ***each tether is able to covalently link more than one growth effector molecule***, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, and	33. A method for growing eukaryotic cells comprising bringing into contact the cells with a compositions comprising 1. a biocompatible solid substrate 2. biocompatible polymeric tethers, and 3. growth effector molecules, wherein one end of each tether is covalently linked to the substrate ***and one end is covalently linked to a growth effector molecule*** so that the growth effector molecule cannot be internalized by cells attached to the substrate; wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell

the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and (b) maintaining the contacting cells and composition under conditions and for a time sufficient to cause the cells to grow; wherein the step of bringing into contact comprises ***administering the composition to a patient in need of cell growth.*** Claims 2-4 further define the route of administration of the composition and the shape and biodegradability of the substrate in the method of claim 1.	growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and ***wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents,*** maintaining the cells in contact with the composition under conditions and for a time sufficient to cause the cells to grow. 14. The method of claim 33 wherein the attachment agent is selected from the group consisting of cyanogens bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, maleimide, and carbodiimide. 15. The method of claim 14 wherein the composition is administered by injection, infusion, or implantation. 16. The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape. 17. The method of claim 16 wherein the substrate is biodegradable.

The claimed compositions of the Cima '828 patent can have other differences. Branched tethers can bind more than one molecule of the same growth effector molecule. This results in the use of lower growth effector concentrations while still achieving receptor aggregation by virtue of the fact that more than one growth effector is linked to each tether. Branched tethers can bind different growth effector molecules on a substrate. This is advantageous if the target cells require the aggregation of different growth effector molecules to enhance cell growth. Further, the use of branched tethers allows for multiple backbone lengths depending on where and how many growth effector molecules are attached. This variety of backbone lengths is important because the presence of ***different*** growth effector molecules may require tethers of different lengths in order to provide the growth effector molecules sufficient mobility to bind to cell surface receptors.

There is nothing in claims 14-17 and 33 that would lead one skilled in the art to substitute branched tethers for the tethers defined in the pending claims. Therefore, claims 1-4 of Cima '828 are not *prima facie* obvious over claims 32 and 34.

Nitecki and Kausch do not disclose the elements missing from claims 1-4 of Cima '828, nor is there any motivation to combine these references. Nitecki and Kausch teach linkers for coupling biological agents, but neither of these suggests that the respective inventions would be useful for growing cells on a biocompatible solid substrate.

Therefore, even if one of ordinary skill in the art was motivated to combine the teachings of Kausch and Nitecki, claims 14-17 and 33 of the present application are not obvious over Cima '828 in view of Kausch and Nitecki.

b. Claims 32 and 34 are obvious over claim 20 of U.S. Patent No. 6,045,818 (Cima '818).

As noted in the Appeal Brief (see pages 19-22), claim 20 of Cima '818 recites a method of testing a compound for an effect on tissue by bringing into contact a compound to be tested and a composition comprising a biocompatible solid substrate, biocompatible branched water soluble polymeric tethers comprising a polymeric material selected from the group consisting of polyethylene oxide, polyvinyl alcohol, polyhydroxyalkyl (meth)acrylate, polyacrylamide, and starches, growth effector molecules, and growing cells. Claims 32 and 34 recite a method of testing a compound for an effect on tissue by bringing into contact a compound to be tested and a composition comprising a biocompatible solid substrate, biocompatible polymeric tethers, growth effector molecules, and growing cells. A side-by-side comparison of the claims is shown below.

'818 Patent: Claim 20	'555 Application-Claims 32 and 34
20. A method of testing a compound for an effect on tissue comprising (a) bringing into contact the compound to be tested and a composition comprising a biocompatible solid substrate, biocompatible ***branched water soluble*** polymeric tethers ***comprising a polymeric material selected from the group consisting of polyethylene oxide, polyvinyl alcohol, polyhydroxyalkyl (meth)acrylate,***	34. A method of testing a compound for an effect on tissue bringing into contact the compound to be tested and a composition comprising a biocompatible solid substrate biocompatible polymeric tethers, and growth effector molecules, and growing cells wherein one end of each tether is covalently linked to the substrate and one end

polyacrylamide, and starches,
growth effector molecules, and
growing cells,

wherein one end of each tether is covalently linked to the substrate, ***each tether is able to covalently link more than one growth effector molecule***, each growth effector molecule is covalently linked to a distal end of a tether so that the growth effector molecule cannot be internalized by cells attached to the substrate, the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules, and

wherein the growing cells are bound to the growth effector molecules;

(b) incubating the compound and the composition under conditions promoting cell growth; and

(c) observing the cells for any effect not observed in cells not brought into contact with the composition,

wherein the substrate is selected from the group consisting of glasses, metals, polystyrenes, polyethylene vinyl acetates, is covalently linked to a growth effector molecule so that the growth effector molecule cannot be internalized by cells attached to the substrate;

wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents; and

wherein the growing cells are bound to the growth effector molecules; incubating the compound and the composition under conditions promoting cell growth; and observing the cells for any effect not observed in cells not brought into contact with the composition.

32. The method of claim 34 wherein the attachment agent is selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, maleimide, and carbodiimide.

polypropylenes, polymethacrylates, polyacrylates, polyethylenes, polyethylene oxides, polysilicates, polycarbonates, polytetrafluoroethylene, fluorocarbons, nylon, silicon rubber, polyanhydrides, polyglycolic acids, polyhydroxyacids, polyesters, polycapralactone, polyhydroxybutyrate, polyphosphazenes, polyorthoesters, polyurethanes, and combinations thereof.	

Like claim 1 of Cima '828, claim 20 of Cima '818 stipulates that each tether is branched and able to covalently link more than one growth effector molecule. However, these claim limitations are not found in claims 32 and 34 of the present application.

Claims 32 and 34 are directed to a method of testing a compound for an effect on tissue by bringing into contact the compound to be tested and a composition comprising a biocompatible solid substrate, biocompatible polymeric tethers, growth effector molecules and growing cells. The composition defined in claims 32 and 34 recites a tether in which the distal end of each tether is linked to a single growth effector molecule. As a result, higher densities of tether and growth effector molecule must be used to enhance the rate of target cell growth over soluble and adsorbed growth effector molecule. Moreover, the length of the tether is of critical importance because it must be sufficient to allow the growth factor a sufficient range of motion to effectively bind to a cell surface receptor. The minimum tether length depends on the nature

of the tether. A more flexible tether (i.e. one without branching) will function well even if the tether length is relatively short.

In contrast, branched tethers have other advantages. Branched tethers can bind more than one molecule of the same growth effector molecule. This allows the use of lower growth effector concentrations while still achieving receptor aggregation by virtue of the fact that more than one growth effector is linked to each tether. Branched tethers can bind different growth effector molecules on a substrate. This is advantageous if the target cells require the aggregation of different growth effector molecules to enhance cell growth. Further, the use of branched tethers allows for multiple backbone lengths depending on where and how many growth effector molecules are attached. This variety of backbone lengths is important because the presence of ***different*** growth effector molecules may require tethers of different lengths in order to provide the growth effector molecules sufficient mobility to bind to cell surface receptors.

There is nothing in claims 32 and 34 that would lead one skilled in the art to substitute branched tethers for the tethers defined in the pending claims. Therefore, claim 20 is not *prima facie* obvious over claims 32 and 34.

Finally, Nitecki and Kausch do not disclose the elements missing from claim 20 of Cima '818, nor is there any motivation to combine these references. As stated above, Kausch and Nitecki teach linkers for coupling biological agents but nowhere in the disclosures of these two patents does it suggest that the respective invention would be useful for growing cells on a biocompatible substrate.

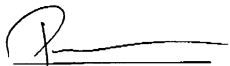
Therefore, even if one of ordinary skill in the art was motivated to combine the teachings of Kausch and Nitecki, claims 32 and 34 of the present application are not obvious over Cima '818 in view of Kausch and Nitecki.

(3) SUMMARY AND CONCLUSION

With respect to the rejections under 35 U.S.C. § 103, the cited prior art references do not teach or suggest methods for enhancing cell growth involving the use of ***water-soluble*** biocompatible polymeric tethers attached to a substrate that is able to bind growth effector molecules so that (1) the molecules cannot be internalized by the cell and (2) the growth rate of target cells is enhanced as compared to the rate of growth of target cells exposed to soluble and adsorbed growth effector molecules.

Moreover, the obviousness-type double patenting rejections are improper because applying the one-way or two-way obviousness test demonstrates that neither the claims in issue nor the claims in Cima '828 or Cima '818 are obvious variations of each other.

Respectfully submitted,



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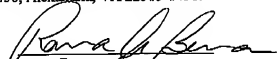
I hereby certify that this Appeal Brief, and any documents referred to as attached therein are being facsimile transmitted on this date June 21, 2004, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.



Ronna Berman

Date: June 21, 2004

Appendix: Claims On Appeal

Claims 1-13 (canceled)

14. (previously presented) The method of claim 33 wherein the attachment agent is selected from the group consisting of cyanogens bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, maleimide, and carbodiimide.

15. (original) The method of claim 14 wherein the composition is administered by injection, infusion, or implantation.

16. (original) The method of claim 15 wherein the composition is administered by implantation of the composition and wherein the substrate is shaped to match a desired tissue shape.

17. (original) The method of claim 16 wherein the substrate is biodegradable.

Claims 18-31 (canceled)

32. (previously presented) The method of claim 34 wherein the attachment agent is selected from the group consisting of cyanogen bromide, succinimide, aldehyde, tosyl chloride, avidin-biotin, epoxide, maleimide, and carbodiimide.

33. (previously presented) A method for growing eukaryotic cells comprising bringing into contact the cells with a compositions comprising

1. a biocompatible solid substrate
2. biocompatible polymeric tethers, and
3. growth effector molecules,

wherein one end of each tether is covalently linked to the substrate and one end is covalently linked to a growth effector molecule so that the growth effector molecule cannot be internalized by cells attached to the substrate;

wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules; and

wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents, maintaining the cells in contact with the composition under conditions and for a time sufficient to cause the cells to grow.

34. (previously presented) A method of testing a compound for an effect on tissue comprising bringing into contact the compound to be tested and a composition comprising

a biocompatible solid substrate,

biocompatible, polymeric tethers,

growth effector molecules, and

growing cells,

wherein one end of each tether is covalently linked to the substrate and one end is covalently linked to a growth effector molecule so that the growth effector molecule cannot be internalized by cells attached to the substrate;

wherein the growth effector molecules are attached to the substrate in a concentration effective to enhance the rate of target cell growth over the rate of target cell growth with soluble growth effector molecules and growth effector molecules adsorbed to a substrate, without internalization of the molecules;

wherein the tether is covalently linked to the substrate and to the growth effector molecule by the same attachment agents; and

wherein the growing cells are bound to the growth effector molecules; incubating the compound and the composition under conditions promoting cell growth; and observing the cells for any effect not observed in cells not brought into contact with the composition.

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